PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 February 2001 (19.02.01)	
International application No. PCT/IT00/00196	**Applicant's or agent's file reference** PCT24373
International filing date (day/month/year) 17 May 2000 (17.05.00)	**Priority date** (day/month/year) 17 May 1999 (17.05.99)
Applicant VALLETTA, Giampiero	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 December 2000 (14.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

IT0000196

Express Mail No.: EL 715 381 313 US

PATENT COOPERATION TREATY

Vienna

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BANCHETTI, Marina
BARZANO' & ZANARDO ROMA S.P.A.
Via Piemonte 26
00187 ROMA
ITALIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	17.08.2001
Applicant's or agent's file reference: PCT24373	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT00/00196	17/05/2000	17/05/1999

Applicant: VALLETTA, Giampiero

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

Form PCT/IPEA/416 (July 1992)

Express Mail No.: EL 715 381 313 US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PCT24373		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IT 00/ 00196	17/05/2000	17/05/1999
Applicant		
VALLETTA, Giampiero		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed. unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

COMBINATION OF NICOTINIC ACID OR NICOTINAMIDE WITH RIBOFLAVIN FOR THE TREATMENT OF PRURITUS, ITCHING AND INFLAMMATION DISORDERS

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ---

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 00/00196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/455 A61K31/525 A61P17/00 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OTROKOV A N: "'New methods of vitamin B treatment of itching dermatoses in middle aged and aged patients!. Novye metody B-vitaminoterapii bol'nykh zudiashchimi dermatozami v pozhilom i starcheskom vozraste." VESTNIK DERMATOLOGII I VENEROLOGII, (1977 DEC) (12) 62-5. , XP000961650 abstract	1-21
X	US 4 619 829 A (MOTSCHAN GEORGES) 28 October 1986 (1986-10-28) column 1, line 35-45 -column 3	1-21
X	FR 2 096 712 A (GIRAUX GEORGES) 25 February 1972 (1972-02-25) claim 2; examples 1,4	1-21

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	22/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 00/00196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 27624 A (LI JUNYAO) 8 December 1994 (1994-12-08) abstract	1-21
A	FUCHS J.: "'Vitamins and skin!. VITAMINE UND HAUT." THERAPEUTISCHE UMSCHAU, (1994) 51/7 (489-495). , XP000961735 page 491 page 493 -page 494	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IT 00/00196

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IT 00/00196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4619829 A	28-10-1986	WO 8401899 A	24-05-1984
		EP 0125252 A	21-11-1984
		JP 5064129 B	14-09-1993
		JP 59502024 T	06-12-1984
FR 2096712 A	25-02-1972	NONE	
WO 9427624 A	08-12-1994	CN 1080855 A	19-01-1994

Express Mail No.: EL 715 381 313 US

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BARZANO' & ZANARDO ROMA S.P.A.
Attn. BANCHETTI, Marina
Via Piemonte 26
00187 ROMA
ITALY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 22/11/2000
Applicant's or agent's file reference PCT24373	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IT 00/00196	International filing date *(day/month/year)* 17/05/2000
Applicant VALLETTA, Giampiero	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest: the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Claudia Aragone

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

Express Mail No: EL 715 381 313 US

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WO 00/69426
PCT/IT00/00196

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
BANCHETTI, Marina
Ing. Barzanò & Zanardo Roma S.p.A.
Via Piemonte, 26
I-00187 Roma
ITALIE

Date of mailing (day/month/year) 23 November 2000 (23.11.00)	
Applicant's or agent's file reference PCT24373	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/IT00/00196	17 May 2000 (17.05.00)	17 May 1999 (17.05.99)

Applicant
VALLETTA, Giampiero

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,DZ,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   23 November 2000 (23.11.00) under No. WO 00/69426

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

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Express Mail No. EL 715 381 313 US

PCT/IT00/00196

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

BANCHETTI, Marina
Ing. Barzanò & Zanardo Roma S.p.A.
Via Piemonte, 26
I-00187 Roma
ITALIE

Date of mailing (day/month/year)
19 February 2001 (19.02.01)

Applicant's or agent's file reference
PCT24373

IMPORTANT INFORMATION

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/IT00/00196	17 May 2000 (17.05.00)	17 May 1999 (17.05.99)

Applicant
VALLETTA, Giampiero

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BR,BY,CH,CU,DK,DM,DZ,EE,ES,FI,GB,GD,GE,GH, GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MW,MX,PT,SD, SG,SI,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Juan Cruz

Telephone No. (41-22) 338.83.38

Express Mail No.: EL 715 [redacted] 313 US

PCT/IT00/00196

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BANCHETTI, Marina
Ing. Barzanò & Zanardo Roma S.p.A.
Via Piemonte, 26
I-00187 Roma
ITALIE

Date of mailing (day/month/year) 05 September 2000 (05.09.00)	
Applicant's or agent's file reference PCT24373	**IMPORTANT NOTIFICATION**
International application No. PCT/IT00/00196	International filing date (day/month/year) 17 May 2000 (17.05.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 17 May 1999 (17.05.99)
Applicant VALLETTA, Giampiero	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
17 May 1999 (17.05.99)	RM99A000309	IT	28 Augu 2000 (28.08.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Somsak Thiphrakesone

Telephone No. (41-22) 338.83.38

Express Mail No. : EL 715 381 313 US

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PCT24373

Box No. I TITLE OF INVENTION: USE OF A VITAMIN COMBINATION FOR THE TREATMENT OF PRURITUS AND NON-INFECTIVE DISORDERS INVOLVING ITCHING AND/OR INFLAMMATION

Box No. II APPLICANT

Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

VALLETTA Giampiero
Via Campidoglio 188
03024 CEPRANO (FR) - ITALY

[X] This person is also inventor

Telephone No. 0775/94186

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: ITALY

State *(that is, country)* of residence: ITALY

This person is applicant for the purposes of: [X] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

[ ] applicant only

[ ] applicant and inventor

[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: [X] agent [ ] common representative

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

BANCHETTI Marina - CAPASSO Olga - de SIMONE Domenico - FIORUZZI Maria Augusta - IANNONE Carlo Luigi - TALIERCIO Antonio - ZANARDO Giovanni - ING. BARZANO' & ZANARDO ROMA S.p.A. - Via Piemonte 26 - 00187 ROMA - ITALY

Telephone No. 06/4743241

Facsimile No. 06/4870273

Teleprinter No. 625579

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

X	AP	ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, TZ Tanzania , ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
X	EA	Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
X	EP	European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
X	OA	OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea,GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other king of protection or treatment desired, specify on dotted line)*

National Patent *(if other king of protection or treatment desired, specify on dotted line):*

X	AE	United Arab Emirates		X	LR	Liberia	
X	AL	Albania		X	LS	Lesotho	
X	AM	Armenia		X	LT	Lithuania	
X	AT	Austria		X	LU	Luxembourg	
X	AU	Australia		X	LV	Latvia	
X	AZ	Azerbaijan		X	MD	Republic of Moldova	
X	BA	Bosnia and Herzegovina		X	MG	Madagascar	
X	BB	Barbados		X	MK	The former Yugoslav Republic of Macedonia	
X	BG	Bulgaria		X	MN	Mongolia	
X	BR	Brazil		X	MW	Malawi	
X	BY	Belarus		X	MX	Mexico	
X	CA	Canada		X	NO	Norway	
X	CH and LI	Switzerland and Liechtenstein		X	NZ	New Zealand	
X	CN	China		X	PL	Poland	
X	CU	Cuba		X	PT	Portugal	
X	CZ	Czech Republic		X	RO	Romania	
X	DE	Germany		X	RU	Russian Federation	
X	DK	Denmark		X	SD	Sudan	
X	DM	Dominica		X	SE	Sweden	
X	EE	Estonia		X	SG	Singapore	
X	ES	Spain		X	SI	Slovenia	
X	FI	Finland		X	SK	Slovakia	
X	GB	United Kingdom		X	SL	Sierra Leone	
X	GD	Grenada		X	TJ	Tajikistan	
X	GE	Georgia		X	TM	Turkmenistan	
X	GH	Ghana		X	TR	Turkey	
X	GM	Gambia		X	TT	Trinidad and Tobago	
X	HR	Croatia		X	TZ	Tanzania	
X	HU	Hungary		X	UA	Ukraine	
X	ID	Indonesia		X	UG	Uganda	
X	IL	Israel		X	US	United States of America	
X	IN	India		X	UZ	Uzbekistan	
X	IS	Iceland					
X	JP	Japan		X	VN	Viet Nam	
X	KE	Kenya		X	YU	Yugoslavia	
X	KG	Kyrgyzstan		X	ZA	South Africa	
				X	ZW	Zimbabwe	
X	KP	Democratic People's Republic of Korea		Check-boxes reserved for designating States (for the purposes of			
X	KR	Republic of Korea		a national patent) which have become party to the PCT after			
X	KZ	Kazakhstan		issuance of this sheet:			
X	LC	Saint Lucia		X	MA	Morocco	
X	LK	Sri Lanka		X	DZ	Algeria	

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 17/05/99 17 MAY 1999	RM99A000309	ITALY		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(Day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	3
description (excluding sequence listing part)	:	23
claims	:	3
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	30

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify):*

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

BANCHETTI Marina

For receiving Office use only

1. Date of actual receipt of the purported international application	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only	
International application No.	
Date stamp of the receiving Office	

Applicant's or agent's file reference PCT24373

Applicant VALLETTA Giampiero.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE	60.000	T	
2. SEARCH FEE	1.829.775	S	

International search to be carried out by _____

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 30 sheets.

rst 30 sheets	791.934	b1	
x _____ = (remaining sheets / additional amount)		b2	
Add amounts entered at b1 and b2 and enter total at B	791.934	B	

Designation Fees

The international application contains _____ designations.

x _____ = (number of designation fees payable *(maximum 10)* / amount of designation fee)	1.363.136	D	
Add amounts entered at B and D and enter total at I	2.155.070	I	

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)*		P	
5. TOTAL FEES PAYABLE	4.044.845		
Add amounts entered at T, S, I and P, and enter total in the TOTAL box	TOTAL		

[ ] The designation fees are not paid at this time.

MODE OF PAYMENT

[ ] authorization to charge deposit account (see below)	[X] bank draft	[ ] coupons
[ ] cheque	[ ] cash	[ ] other *(specify)*:
[ ] postal money order	[ ] revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____

[ ] is hereby authorized to charge the total fees indicated above to my deposit account.

[ ] is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

[ ] is hereby authorized to charge the fees for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No.	Date *(day/month/year)*	Signature

Express Ma[redacted] No.: EL 715 381 313 US

PATENT COOPERATION TREATY

S Vicent

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
BANCHETTI, Marina
BARZANO' & ZANARDO ROMA S.P.A.
Via Piemonte 26
00187 ROMA
ITALIE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	25. 01. 01
Applicant's or agent's file reference: PCT24373	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ IT 00/ 00196	17/05/2000	17/05/1999

Applicant: VALLETTA, Giampiero

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

14/12/2000

2. This date of receipt is:

- [X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

[ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	MORENO R A Tel. (+49-89) 2399-2658

EUROPÄISCHES PATENTAMT · EUROPEAN PATENT OFFICE · OFFICE EUROPÉEN DES BREVETS

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PCT24373		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IT 00/ 00196	17/05/2000	17/05/1999
Applicant		
VALLETTA, Giampiero		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   COMBINATION OF NICOTINIC ACID OR NICOTINAMIDE WITH RIBOFLAVIN FOR THE TREATMENT OF PRURITUS, ITCHING AND INFLAMMATION DISORDERS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ---

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 00/00196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/455 A61K31/525 A61P17/00 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OTROKOV A N: "'New methods of vitamin B treatment of itching dermatoses in middle aged and aged patients!. Novye metody B-vitaminoterapii bol'nykh zudiashchimi dermatozami v pozhilom i starcheskom vozraste." VESTNIK DERMATOLOGII I VENEROLOGII, (1977 DEC) (12) 62-5. , XP000961650 abstract	1-21
X	US 4 619 829 A (MOTSCHAN GEORGES) 28 October 1986 (1986-10-28) column 1, line 35-45 -column 3	1-21
X	FR 2 096 712 A (GIRAUX GEORGES) 25 February 1972 (1972-02-25) claim 2; examples 1,4	1-21

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	22/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 27624 A (LI JUNYAO) 8 December 1994 (1994-12-08) abstract ---	1-21
A	FUCHS J.: "'Vitamins and skin!. VITAMINE UND HAUT." THERAPEUTISCHE UMSCHAU, (1994) 51/7 (489-495). , XP000961735 page 491 page 493 -page 494 -----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IT 00/00196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4619829 A	28-10-1986	WO 8401899 A	24-05-1984
		EP 0125252 A	21-11-1984
		JP 5064129 B	14-09-1993
		JP 59502024 T	06-12-1984
FR 2096712 A	25-02-1972	NONE	
WO 9427624 A	08-12-1994	CN 1080855 A	19-01-1994

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCT24373		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT00/00196	17/05/2000	17/05/1999
International Patent Classification (IPC) or national classification and IPC A61K31/455		
Applicant VALLETTA, Giampiero		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/12/2000	17.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giacobbe, S Telephone No. +49 89 2399 8463

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT00/00196

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

2-7,9,11,13, 15-23	as originally filed			
1,8,10,12,12a,14, 14a	as received on	21/05/2001	with letter of	21/05/2001

Claims, No.:

1-21	as received on	21/05/2001	with letter of	21/05/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 8-15 (IA only).

because:

   ☒ the said international application, or the said claims Nos. 8-15 (IA only) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	16-21
Inventive step (IS)	Yes:	Claims	1-15

	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-7, 16-21
	No:	Claims 8-15 (see Separate Sheet)

2. Citations and explanations
see separate sheet

1. Section I

The amended claims do not fulfill the requirements of Art 34(2)(b) PCT since the two disclaimers introduced in each of the independent claims 1, 8 and 16 are by far broader than the scope of the prior art documents D1-D4. For example, the expression "any other anti-inflammatory agent" comprises e.g. also aspirin, whereas document D3 is limited to the presence of a steroidal anti-inflammatory agent. Analogously document D1 discloses only compositions where only the vitamins of the B group are (simultaneously) present, not just "any other vitamin agent". The attention of the Applicant is further drawn to the fact that disclaiming diseases cannot establish the novelty of claim 16 (a "composition claim"), since once a composition is known in the medical field only its further medical use can be patented.

The present report has been established based on the originally filed claims.

2. Section III

Claims 8-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). However, although not required under the provisions of the PCT, an opinion will be given with respect to novelty and inventive step.

3. Section V

3.1 Cited Documents

The following documents (D) are referred to in this Report:

D1: OTROKOV A N: 'Novye metody B-vitaminoterapii bol'nykh zudiashchimi dermatozami v pozhilom i starcheskom vozraste.' VESTNIK DERMATOLOGII I VENEROLOGII, vol. 12, 1977, pages 62-65

D2: US-A-4 619 829 (MOTSCHAN GEORGES) 28 October 1986

D3: FR-A-2 096 712 (GIRAUX GEORGES) 25 February 1972

D4: WO 94 27624 A (LI JUNYAO) 8 December 1994

Unless otherwise noted, reference is made to the passages quoted in the Search Report.

3.2 Art 33(2) PCT (Novelty)

3.2a The subject-matter of present claims 16-21 does not meet the requirements of Art 33(2) PCT.

Document D4 discloses compositions containing, as active agents, vitamins B2 and PP. The particular intended use of these compositions is the treatment of cancer. This document is therefore novelty-destroying for claims 16-21.

3.2b The subject-matter of present claims 1-15 meets the requirements of Art 33(2) PCT.

This IPEA is of the opinion that the expression "use of a combination of..." *per se* (cf. claim 1) does not necessarily mean that only the listed active ingredients are present. However, in the present case a careful reading of claims 8 and 16 (cf. the expression "containing, as active agents") makes it clear that exactly this is meant by the aforementioned expression (although the expression "as sole active agents" after riboflavinwould have helped in understanding the scope of the claim). The following considerations concerning documents D1-D3 therefore apply:

i) document D1 discloses the use of preparations containing Vitamin B2 (Riboflavin) and PP (Nicotinamide) for the treatment of itching dermatoses. These compositions, according to the provided translated version of the document, also contain two other members of the Vitamin B complex as active agents, and therefore this document is not considered as novelty-destroying.

ii) document D2 discloses the use of polyvitamin preparations containing *inter alia* vitamins B2 and PP (cf. Examples) for systemic, oral, parenteral or topical administration for the treatment of inflammatory rheumatic diseases. For the same reason as above this document is not considered as novelty-destroying.

iii) document D3 discloses the use of preparations containing vitamins B2 and PP and a steroidal anti-inflammatory agent for the treatment of pruritus (cf. p. 1, l. 36). For the same reason as above this document is not considered as novelty-destroying.

3.3 Art 33(3) PCT (Inventive step)

The subject-matter of present claims 1-15 meets the requirements of Art 33(3) PCT since it overcome the technical prejudice established by document D3 (cf passage

bridging pages 2 and 3), namely that riboflavin and niacin alone (i.e. in the absence of a steroidal anti-inflammatory agent) are not able to treat the prurit associated with skin diseases. Also documents D1 and D2 cannot take away the inventiveness of this subject-matter, since their teaching is that four members of the B complex (vitamins B1, B2, PP and B6) are necessary for achieving the desired therapeutic effect.

3.4 Art 33(4) PCT (Industrial applicability)

As stated above, no opinion is given on the question of whether present claims 8-15 are industrially applicable since their patentability is inter alia dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.

USE OF A VITAMIN COMBINATION FOR THE TREATMENT OF PRURITUS AND NON-INFECTIVE DISORDERS INVOLVING ITCHING AND/OR INFLAMMATION

SPECIFICATION

The present invention concerns the use of a vitamin combination for the treatment of pruritus and non-infective disorders involving itching and/or inflammation. More particularly, this invention relates to the use of a combination of two vitamin compounds, i.e. riboflavin (also known as vitamin B_2) and nicotinic acid (also referred to as niacin) or, as an alternative thereto, the corresponding amide, i.e. nicotinamide or niacinamide (also known as vitamin PP) for the systemic treatment of various forms of itching, such as, e.g., pruritus associated with renal insufficiency or failure, or forms of itching the etiology of which is not connected with organic lesions or with other primary pathologies, as well as for the treatment of a number of non-infective internal affections of a substantially inflammatory nature.

As it is known, the cutaneous sensation currently referred to as itching may be considered as a uniform response to a wide variety of physical and chemical stimuli, which may be of an endogenous or exogenous nature. Such stimuli act on the receptors of the free nerve endings located at the dermal-epidermal junction and around the hair follicles. It is currently believed that pain, temperature and touch are all sensations transmitted through the same pathways of non-myelinated free nerve fibers innervating human skin. A low-intensity stimulation of such fibers would cause pruritus while a more intense stimulation would turn into a real pain sensation. While being transmitted through the same sensory fibers, the neural impulses of itch have a frequency quite lower than the pain impulses; however, if scratching follows as a response to the itch stimulus, the frequency of the neural impulses increases with the intensity of scratching, and the corresponding sensation turns from itchy into painful.

It has been found, however, that the desired effect is obtained when niacin or nicotinamide are administered systemically in combination with another known vitamin compound, i.e. riboflavin or vitamin B_2.

In this connection, the U.S. Patent No. 5,496,827 teaches compositions for topical application on the skin, wherein the main active ingredient, i.e. methyl nicotinate, may be combined with various vitamins, minerals and other nutrients, including, inter alia, riboflavin. The resulting topical compositions are proposed for use in the treatment of various conditions that may be treated by means of topical applications to the affected areas, such as muscular pain, acne, eczema, or for stimulating the hair growth, removing senile lentigines (brown spots) and enhancing fingernail growth. Also in this case, the prior art points out that an excessive increase of the methyl nicotinate level "tends to produce a rather pronounced pruritus (itching of the skin)". The concerned document, however, mentions riboflavin as one of the many vitamins and trace elements that may be added to methyl nicotinate in order to be carried through the skin by transdermal delivery, as the alleged function of methyl nicotinate is to promote transdermal delivery.

With reference to the second active ingredient of the present invention, i.e. riboflavin (7,8-dimethyl-10-(D-ribo-2,3,4,5-tetrahydroxypenthyl)isoalloxazine, also such compound is a nutritional factor of a primary importance, that is found mainly in milk, eggs, cheese, liver, heart, kidney and leafy vegetables. Riboflavin carries out its biological function in the body in the form of one or the other of two coenzymes, i.e. riboflavin phosphate, commonly called flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD). Similarly to the two pyridine coenzymes referred to in the foregoing (i.e., NAD and NADP), FMN and FAD co-operate with the respiratory flavoproteins in oxidizing the substrate by accepting a hydrogen molecule from the substrate. Contrary to NAD and NADP, however, FMN and FAD may yield said hydrogen directly to molecular oxygen. In addition, the oxidoreductive potential of FMN and FAD is such that these two compounds can oxidize the reduced pyridine coenzymes: actually, the function of flavoproteins (having, as pointed out before, FAD and FMN as coenzymes) is on one hand to directly oxidize the

In view of the foregoing, in the light of the clinical tests results presented further on, it may reasonably be postulated that both the "sine materia" pruritus forms, which are not due to any primary dermatological or internal affection, and uremic pruritus, which is a manifestation of unknown etiology connected with renal insufficiency, are caused by some energy-controlled alterations in the metabolic pathway leading to the secretion of biochemical mediators from mast cells, and that the systemic administration of a suitable dosage of niacin or nicotinamide and riboflavin would provide the body with the necessary amounts of NAD/NADP and FAD/FMN to properly modulate the mast cells activity.

As a further object of the instant invention, other affections of a non-infective etiology characterized by itching and/or inflammation (phlogosis) such as, e.g., urticaria and angioedema, bronchial asthma, allergic rhinitis and oculorhinitis, have been considered, in the light of the above etiopathogenetic theory, in order to provide a systemic therapy exploiting the same combination of active ingredients.

As it is known, urticaria is a pruritic dermatosis characterized by the formation of circumscribed, raised, erythematous and usually pruritic areas of edema. Such lesions have a rosy-red appearance with a white central area, and are surrounded by an erythematous halo. The single wheals may have a round, elliptic or variously contoured shape, and may evolve in a few days or weeks (acute urticaria) or in several weeks or months (chronic urticaria). When the edematous process extends into the dermis and/or subcutaneous or submucosal layers, the relevant affection is known as angioedema. Urticaria and angioedema may occur in any position together or individually. Both affections may be due to several etiologic factors of an immunologic nature (such as, e.g., hypersensitivity to pollens, foods, drugs, etc.), or of a non-immunologic nature (e.g. non-IgE-dependant intolerance to various therapeutic and diagnostic agents, such as the well-known reactions to aspirin and related non-steroidal anti-inflammatory agents). However, in the great majority of cases, urticaria/angioedema is of unknown cause, and is currently referred to as idiopathic urticaria.

combination of nicotinic acid or nicotinamide with riboflavin for the manufacture of a medicament not comprising as the active ingredients any other anti-inflammatory agent or any other vitamin agent besides said nicotinic acid or nicotinamide and said riboflavin, said medicament being suitable for systemic administration, for the treatment and/or the prophylaxis of pruritus and non-infective, non-neoplastic, non-rheumatic disorders involving itching and/or inflammation. Specifically, the forms of pruritus against which the proposed combination is particularly effective include itch associated with renal insufficiency or failure (i.e. uremic pruritus) and pruritus forms that are not connected with primary organic affections, such as itching of aged skin (i.e., senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus. As to the non-infective disorders involving itching and/or inflammation, the proposed combination is particularly useful for combating urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

For the therapeutic indications according to the present invention, the two active ingredients are to be systemically administered at a dosage comprised between 0.5 and 750 mg/day of niacin or of nicotinamide and between 0.1 and 250 mg/day of riboflavin. Preferably, the said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin), optionally in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration. The preferred ratio is 20:1 (niacinamide : riboflavin). According to a particularly effective therapeutic protocol, 50 mg of nicotinamide + 2.5. mg of riboflavin are orally administered twice daily, and the treatment is continued until the itching or the inflammatory affection has totally disappeared. Thereafter, in some particular instances, the treatment is continued with half the dosage of the vitamin combination, for about 15 more days.

The compounds according to the invention may be administered through different systemic routes, e.g. orally or parenterally. For such types of administration the active ingredients may be incorporated in conventional pharmaceutical preparations, in solid or liquid dosage forms. The latter may contain the adjuvants usual in the pharmaceutical art such as, for instance,

sweeteners, flavors, colors, coatings and preservatives, inert diluents such as calcium carbonate, sodium carbonate, lactose and talc, binders such as starch, gelatin and polyvinylpyrrolidone, suspending agents such as methyl

namide and 1 mg of riboflavin once or twice daily.

According to another specific aspect thereof, the present invention provides a composition for systemic administration for the treatment and/or the prophylaxis of pruritus and non-infective, non-neoplastic, non-rheumatic disorders involving itching and/or inflammation, containing, as the active ingredients, a combination of nicotinic acid or nicotinamide with riboflavin and free from any other vitamin agent and any other antiinflammatory agent besides said nicotinic acid or nicotinamide and said riboflavin. Particularly preferred features of the said compositions are recited in the dependent claims. It is evident, however, that the two active ingredients of the invention do not necessarily have to be contained in a single preparation, as they can be administered separately, provided that the dosage and therapeutic protocol are as prescribed in the foregoing.

Some experimental results obtained according to the present invention, including clinical data concerning the performance of the proposed combination in comparison with the use of nicotinic acid or nicotinamide alone, are reported below for merely illustrative purposes.

1st series of tests - Treatment with the nicotinamide-riboflavin combination

1st case - 67-year-old male subject in renal dialysis three times weekly - At the start of the test, the patient had been on dialysis three times a week for about two years, each treatment lasting 4 hours. For about 4 years, the patient had been complaining of a diffused itching. The latter was quite moderate at the beginning, but had been gradually increasing in intensity, and had become quite unbearable. Upon interviewing the specialists responsible for the renal treatment, he was given antihistamines for about six months with no appreciable result. As a consequence, the patient had discontinued the antihistamine treatment.

Thereafter, the patient was treated with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, by oral administration. After 5 days from the start of this therapy, itching had disappeared. The patient continued the same therapy for about 15 days, and thereafter the dosage was reduced to one-half, the

administration occurring after the dialysis treatment. The subsequent checks, performed every month, showed that itching had totally disappeared.

CLAIMS

1. Use of a combination of nicotinic acid or nicotinamide with riboflavin for the manufacture of a medicament not comprising as the active ingredients any other antiinflammatory agent or any other vitamin agent besides said nicotinic acid or nicotinamide and said riboflavin, said medicament being suitable for systemic administration, for the treatment and/or the prophylaxis of pruritus and non-infective, non-neoplastic, non-rheumatic disorders involving itching and/or inflammation.

2. Use according to claim 1, wherein said medicament is for the treatment and/or the prophylaxis of pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections.

3. Use according to claim 2, wherein said pruritus forms that are not connected with primary organic affections are chosen from the group consisting of itching of aged skin (i.e. senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus.

4. Use according to claim 1, wherein said medicament is for the treatment and/or the prophylaxis of a disorder chosen from the group consisting of urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

5. Use according to any one of claims 1-4, wherein said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin), optionally in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration.

6. Use according to claim 5, wherein said combination consists of nicotinamide and riboflavin in a ratio by weight of 20:1.

7. Use according to any one of claims 1-6 for the manufacture of a medicament for oral or parenteral administration.

8. A method for the treatment and/or the prophylaxis of pruritus and non-infective, non-neoplastic, non-rheumatic disorders involving itching and/or

inflammation in a subject in need of the same, which method comprises systemically administering to the said subject an effective amount of nicotinic acid or nicotinamide and an effective amount of riboflavin, and excludes administering any other vitamin agent and any other antiinflammatory agent besides said nicotinic acid or nicotinamide and said riboflavin.

9. The method according to claim 8, wherein said medicament is for the treatment and/or the prophylaxis of pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections.

10. The method according to claim 9, wherein said pruritus forms that are not connected with primary organic affections are chosen from the group consisting of itching of aged skin (i.e. senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus.

11. The method according to claim 8, wherein said medicament is for the treatment and/or the prophylaxis of a disorder chosen from the group consisting of urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

12. The method according to any one of claims 8-11, comprising systemically administering to the said subject an effective amount of a combination of nicotinic acid or nicotinamide and riboflavin, optionally in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration.

13. The method according to claim 12 wherein said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin).

14. The method according to claim 13, wherein said combination consists of nicotinamide and riboflavin in a ratio by weight of 20:1.

15. The method according to any one of claims 8-14, wherein said systemic administration is by the oral route or by the parenteral route.

16. A composition for systemic administration for the treatment and/or the prophylaxis of pruritus and non-infective, non-neoplastic, non-rheumatic disorders involving itching and/or inflammation, containing, as the active ingredients, a combination of nicotinic acid or nicotinamide with riboflavin and

free from any other vitamin agent and any other antiinflammatory agent besides said nicotinic acid or nicotinamide and said riboflavin.

17. The composition according to claim 16, for the treatment and/or the prophylaxis of pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections.

18. The composition according to claim 17, wherein said pruritus forms that are not connected with primary organic affections are chosen from the group consisting of itching of aged skin (i.e. senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus.

19. The composition according to claim 16, for the treatment and/or the prophylaxis of a disorder chosen from the group consisting of urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

20. The composition according to any one of claims 16-19, wherein said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin), in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration.

21. The composition according to claim 20, for oral administration or for parenteral administration.

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(54) Title: MINERAL AND VITAMIN COMBINATIONS FOR THE TREATMENT OF STRESS AND ALLERGIES

(57) Abstract

The treatment is by means of nutritional supplements for the adrenal glands, liver and mast cells. The supplements may include potassium, magnesium, Vit B_6, Vit B_5, Vit C and EFA. A biological mechanism linking stress and allergies such as hayfever or other perennial or seasonal respiratory allergies is proposed and the effect of the treatment thereon is discussed.

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MINERAL AND VITAMIN COMBINATIONS FOR THE TREATMENT OF STRESS AND ALLERGIES

Field of Invention

This invention relates to novel treatments for allergies such as hayfever and other seasonal and perennial respiratory allergies which the inventor believes are triggered by stress.

The Invention

The invention is set out in the claims herein but simply stated the inventor has devised a method of treating stress and/or allergies, such as hayfever and other seasonal or perennial respiratory allergies, by the co-administration, either simultaneously or sequentially, of ingredients comprising potassium, magnesium, Vit B_6, Vit B_5, Vit C and an n-6 or n-3 essential fatty acid (EFA) particularly GLA or DGLA. These ingredients (hereinafter "active ingredients") alone are effective but optionally may be combined with other synergistic nutrients.

The invention also extends to compositions comprising those active ingredients in unit dosage form, effective in the treatment of those conditions, and the use of those active ingredients in the manufacture of a medicament, as a single composition or as sub-compositions for co-administration, for treatment of those conditions. The method composition and use of the invention may be applied to the treatment of a human or non-human (preferably mammalian) animal body.

The active ingredients may be present in combination with any pharmaceutically acceptable carrier and may be in any assimilable form for any particular ingredient as well known to those skilled in the art.

In one embodiment the composition comprises the active ingredients in capsule or other form in amounts as follows, and was administered in daily doses :

Potassium Gluconate	10mg to 5000mg preferably 100mg to 1000mg and very preferably 100mg to 400mg.
Magnesium Oxide	1.0mg to 1000mg preferably 10mg to 500mg and very preferably 50mg to 300mg.
Pyridoxine Hydrochloride (Vit B_6)	0.1mg to 500mg preferably 5mg to 200mg and very preferably 10mg to 100mg.
Pantothenic Acid (Vit B_5)	0.1mg to 1000mg preferably 10mg to 500mg and very preferably 50mg to 300mg.
Ascorbic Acid (Vit C)	10mg to 5000mg preferably 100mg to 2000mg and very preferably 500mg to 1000mg.
GLA, for example from Evening Primrose Borage or Blackcurrant	10mg to 5000mg preferably 100mg to 2000mg and very preferably 400mg to 1000mg.

The following are synergistically supporting ingredients which optionally may be included in the formula:

Fish Oils to supply n-3 EFAs; Vitamins selected from Vit B_1 Thiamine; Vit B_2 Riboflavin; Folic Acid; Vit B_{12} Cyanocobalamin; Vit B_3 Niacinamide; Vit A Beta Carotene; Vit D Ergocalciferol; Vit E; Biotin; Bioflavonoids; Choline; Inositol; and minerals and trace elements selected from bioavailable forms of Boron; Phosphorus; Manganese; Sodium; Copper; Iron; Zinc; Calcium; Selenium.

The composition may provide the six primary active ingredients alone or may provide these together with one or more of the listed optional minerals and other materials important in the

stress response. Vit E may optionally be given in a daily dose of 1mg to 600mg, preferably 10mg to 400mg and very preferably 10mg to 50mg.

The compositions according to the invention may be administered in any convenient form known to those skilled in the art. These forms include capsules of various types, powders, tablets, solutions, suspensions, emulsions and aerosol sprays. The composition may be administered orally, enterally, parenterally or transdermally using appropriate technology known to those skilled in the art. For complete and effective control of allergic symptoms, the composition is intended for administration on a daily basis.

Further preferred features of the invention are in the dependent claims. An illustrative treatment regimen embodying the invention and what is believed to be a possible underlying physiological mechanism are described below with reference to the drawings in which:-

Fig. 1 is a simplified flow diagram showing the interaction of adrenal stress response with the liver and mast cells;

Fig 2(a) shows the normal antigen response at cellular level, and

Fig 2(b) shows the allergic response at sensitised mast cell level.

Example

The following formula was administered to volunteers and after 4 days of ingestion was completely successful in eliminating all allergic symptoms:-

Potassium as gluconate	408 mg
Evening Primrose Oil (10% GLA)	500 mg
Vit C	530 mg
Bioflavonoids	25 mg
Magnesium as oxide	134 mg

Vit B_6 Pyridoxine	50 mg
Vit B_5 (d-pantothenic acid)	50 mg
Vit B_1 (thiamine)	5 mg
Vit B_2 (riboflavin)	5 mg
Bioavailable Zinc	8 mg
Bioavailable Manganese	2 mg
Bioavailable Selenium	25 µg
Bioavailable Chromium	25 µg

Withdrawal of treatment led to a return of symptoms within an average of seven days.

The following considers the allergic response to toxic stress, induced by an abnormal biochemical response to antigens and elucidates a therapeutic nutritional approach, designed to counteract the biochemical effects of toxic stress. Whether or not the theory on which the formulation is based is correct, the inventor has found this approach to be effective in treating respiratory allergy and its full range of symptoms.

Proposition

Allergies such as perennial and seasonal respiratory allergies may be caused by nutritional deficiency precipitated by toxic stress, resulting in an impaired immune response which reacts abnormally to innocuous antigens. Compositions and methods of treatment according to the invention are designed to supplement nutrient levels to combat stress in three active sites: the adrenal glands, liver and mast cells.

Stress

Stress which applies any sort of biological pressure upon the body has a number of origins e.g. chemical pollution, emotional, hormonal, viral and bacterial disease. Social pressures upon individuals, present levels of pollution (i.e. airborne, chemicals in agriculture and food manufacture, industry, internal combustion engines), plus naturally occurring toxins in the metabolism invoke a stress reaction. This in turn can trigger a number of physical disorders

including an autoimmune reaction where the thyroid, adrenal cortex and joints are often affected. Also an individual may become prone to allergies.

The Biochemical Stress Reaction

Stress causes a biochemical reaction which is both toxic and disruptive to the metabolism. Biochemical stress of any sort provokes adrenal gland activity (figure 1). The adrenal glands require sugar energy to combat stress. This is obtained by cytolysis and proteins are destroyed. Initially sacrificial proteins in the thymus and lymph glands are utilised; thereafter sugar is obtained by a general invasion of any available proteins. The by-product of this ongoing cell death is histamine, which the liver neutralises with histaminase.

Frequent or prolonged stress, at any level of severity, prompts the adrenal glands to take defensive action and makes heavy demands upon available nutrients, which they provision from the bloodstream, bones, soft tissues and major organs, including the liver. An important function of the liver is the de-toxification of the bloodstream. It is also a major factor in the immune system. Sustained adrenal stress creates demands upon the liver, which sets up a degrading nutrient spiral, as liver nutrients are acquisitioned by the adrenal activity and also expended in the detoxification process. In this 'stage of resistance' to stress, if all available nutrients are expended, and insufficient nutrients provisioned by diet, the adrenal glands can become exhausted and the liver can be damaged. With insufficient nutrient availability, the adrenal glands cease to function, the liver is unable to regenerate itself or maintain its vital functions, the immune system is impaired, important biochemical processes are impeded and the body is rendered susceptible to disease.

Stress And Respiratory Allergy

The Mast Cell

The mast cell is situated in the skin and mucous membranes. It is the body's first defence against external antigens. Its function is to trap and then assist in the destruction of invading organisms and foreign proteins which could harm the biochemistry of the body. Figure 2a is

a simplified illustration of the sequence of responses to antigens at cellular level in a non-allergic state. In order to defend itself, the mast cell has a double membrane heavily fortified by phospholipids (supplied by the liver). This double membrane becomes permeable and subject to invasion by foreign proteins, if not liberally supplied with nutrients, including these phospholipids.

Intracellular Environment

The intracellular pH and composition of the mast cell is under the control of potassium. Potassium is needed by the adrenal glands in large quantity during the stress resistance stage and is utilised in glycolysis to provide sugar energy. The adrenals also require supplies of lipids. As mast cells exist in abundance, they may be an easily obtainable source of potassium and lipids for the adrenal gland stress response. It is notable that the potassium and lipid content of the mast cell is crucial to its function and survival and depletion will have a profound impact.

Sodium and Potassium

Potassium largely resides intracellularly, while sodium is normally present extracellularly. These two cations exist in roughly equal proportion. Sodium and potassium are antagonistic towards each other and an abundance of one will drive out the other.

Membrane permeability

The mast cell membrane will become 'brittle' and rendered markedly more permeable by insufficient phospholipids. This allows sodium and calcium to be transported across the bi-membrane and into the intracellular environment, driving out potassium and magnesium, which is the first stage in the allergic cascade. Cell disruption results for the following reasons:-

a. With few exceptions, most enzymes cannot tolerate sodium. Therefore, within the mast cell, normal enzymatic activity is impeded.

b. Intracellular potassium is responsible for carbohydrate and protein metabolism and enzymatic reactions including the hydrolysis of ATP, which actively controls the transport of ions across the cell membrane.

When potassium is displaced by sodium, all of these biochemical processes are disrupted. Aldosterone, produced by the adrenal glands in the stress reaction is responsible for the retention of sodium and water which drives out potassium. Therefore, confronted with antigen, under adrenal stress conditions, a sensitised mast cell may be already rendered susceptible to intracellular invasion because of:-

(a) adrenal stress nutrient demands (including intracellular potassium and membrane lipids)

(b) sodium displacement of potassium, as a result of aldosterone activity.

Either of these events will have a profound effect. As intracellular potassium is removed/expelled, sodium, water and calcium enter to replace it. This results in acute cellular oedema which effects a pH alteration. The cell structure, including the bi-membrane, alters in shape and cytoskeletal organisation. This process is reversible via the sodium pump and if the cell's oxygen supply is brought back to normal.

It seems probable that activity of the antigen/IgE coupling, under these conditions, would find the mast cell vulnerable and completely unable to defend itself. Furthermore, the cellular oedema may lower pH to a level which is exactly suitable for the histidine/histamine conversion. And if the enzyme histidine carboxylase, which converts histidine to histamine, happens to be one of the few enzymes unaffected by sodium, this may cause the mast cell to enter a state of irreversible cytotoxicity, degranulate and release its own toxins, primarily histamine, which result in the allergic reaction. Therefore allergic respiratory disease is perhaps the end result of a biochemical chain reaction within the body, in which the mast cell is attacked on two levels, endogenously by the stress reaction and externally by antigen. (Figure 2b).

The allergic reaction

Traditionally, antihistamine medicaments have formed the basis of medical therapy. These medicaments aim to treat the symptoms of the acute stage of allergic reaction, by blocking the release of histamine in an attempt to circumvent the allergic cascade, but do not aspire to eradicate the disease. The inventor's approach is founded upon nutritional supplementation, which aims to satisfy stress derived nutrient demands and reinforce the body's immune system; thereby allowing this defensive biochemistry to deal with antigens efficiently, as it naturally does in non-allergic individuals. However, it has been found that such reinforcement takes time to reach optimum effect. Typically, a daily ingestion of a composition embodying the invention for 3-4 days is necessary, whereafter all allergic reaction symptoms cease.

The medically accepted cause of an allergic reaction may be defined as follows:-

> An allergic reaction occurs due to the excessive immune response to some non-threatening foreign protein, initiated when IgE bearing B cells are activated by antigen to secrete IgE antibody. These bind mast cells and basophils resulting in degranulation and release of histamine and other potent mediators causing allergic symptoms such as long term inflammatory effects. Allergic symptoms result from the overwhelming release of histamine and other mediators into the biochemistry of the body.

In answer to the question why some individuals become allergic when others do not, it is suggested here that the mast cell's intrinsic nutritional state of readiness to deal with antigen is a major contributor in resistance to antigen, or conversely in initiation of the allergic cascade. It is further suggested that the nutritional state of the adrenal glands and the liver will mediate the degree of severity of the allergic cascade at mast cell level. The liver supplies vital nutrients to both adrenals and mast cells and detoxifies the bloodstream. The sacrificial mast cell is the first line of defence against invasion of antigens. It may also be first in line as a readily available source of lipids and potassium. Any disruption of adrenal or liver function will affect the mast cell's nutrient status and defensive capability. The biochemical response

to the effect of allergen invasion at each of these sites will be governed by their nutritive state. If well supplied with the essential nutrients, these three sites, in concert, will neutralise the allergen and its toxic potential and establish a state of tolerance. A healthy adrenal system will produce adequate cortisone. A healthy liver will support the immune system and produce adequate histaminase to neutralise any histamine produced in reaction to the stress. A healthy mast cell has sufficient phospholipids (supplied by the liver) to maintain correct permeability of its membrane in order to defend itself from abnormal biochemical alteration. This alteration may be the result of penetration by the allergen/IgE chemotactic signal or the adrenal stress effects upon its biochemistry.

The methods and composition of the invention are intended to supplement nutrient requirements and hence may:-

(a) reduce mast cell membrane permeability,

(b) supply appropriate nutrients to encourage 'normal tolerance' to antigen.

(c) maintain favourable pH levels in the mast cell.

(d) supply sufficient nutrients to the adrenal glands in order to serve the stress reaction, including potassium for glycolysis.

(e) supply the liver with nutrients to maintain adequate function to serve the immune system.

By addressing the nutrient requirements of the adrenal glands, the formula minimises the burden of nutritional provision by the liver, thus allowing this organ to continue to utilise its stocks in support of the immune system (including the mast cell), thereby enhancing immunity and assisting in establishing 'normal tolerance to antigen' in the mast cell. As demonstrated in strictly confidential tests upon volunteers, this approach appears wholly effective in completely eliminating all symptoms of allergic respiratory conditions. The composition is equally effective in seasonal and perennial forms of this condition. Further, it has been noted that allergic individuals sense of smell and taste was also restored, even after years of sensory impairment. Also, subjects taking the composition on a daily basis have entered highly allergenic environments with no ill effects whatsoever. Even those with extremely long term perennial allergies (i.e. 20 years plus) are able to come into contact with known allergens without suffering any allergic reaction.

While it is accepted that the foregoing hypothesis must be independently tested and clinically proven, it is the suggestion of the inventor that the biochemical consequences of stress may be a primal cause in allergic reactions. The success of the composition in completely eliminating all symptoms of allergic reaction in sensitive individuals, may demonstrate that it is not inevitable that an allergen sensitised mast cell is constrained to enter the cytototoxicity/degranulation/histamine release cycle.

The composition is designed to address substantially the whole process of the allergic reaction, cause and effect, within the major sites involved, i.e. adrenal glands, liver and mast cell in the case of hayfever. An appropriately modified balance of the active ingredients may be effective in treating other allergic conditions, some of which are allergic asthma, urticaria, hives, eczema, psoriasis and allergic conjunctivitis. For instance, in the case of eczema and psoriasis, it would be expected to increase the percentage of EFA, Vit C, Vit B_6 and the minerals magnesium and zinc, with respect to the example given above, which is formulated primarily for the treatment of hayfever and Vit E will specifically be added. With allergic asthma, it may be appropriate to increase Vit B_6, Vit C and magnesium.

The composition and treatment method has also been tested on horses suffering from chronic obstructive pulmonary disease ("stable cough": an allergy to dust and moulds found in hay), laminitis ("founder": an allergy to histamines in grass) and allergic eczema("sweet itch": an allergic reaction to biting insects). Doses were calculated according to body weight and administered daily. In all cases symptoms were reduced and controlled within four days and eradicated within seven days. This would suggest that organic allergic reactions in all mammalian bodies may respond favourably to the composition and treatment method.

Furthermore, as this therapeutic nutritional approach is predicated upon counteracting the biochemical effects of toxic stress, the model offered may be applicable to the management of all stress related diseases. Although it is not suggested here that the composition is a complete nutritional supplement, it is suggested that a suitably modified formulation of the stated ingredients would be an appropriate daily nutritional supplement to be taken

prophylactically against all forms of existing and anticipated stress. It is further suggested that the composition may be beneficial if taken concurrently with medicaments prescribed for symptom control of stress induced diseases, such as arthritis and essential hypertension (not caused by atherosclerosis or renal failure), with the expectation that the composition would biochemically ameliorate the stress effect, which underlies the disease. This, in turn, may effect a reduction / cessation of symptoms.

Claims

1. Use of potassium and magnesium as minerals, Vit B_6, Vit B_5, Vit C and an n-6 or n-3 essential fatty acid (EFA), particularly GLA or DGLA, in the manufacture of a medicament, as a single composition or as sub-compositions for co-administration, for treatment of stress and/or allergies particularly hayfever and other seasonal and perennial respiratory allergies.

2. A method of treating stress and/or allergies, particularly hayfever and other seasonal and perennial respiratory allergies, wherein potassium and magnesium as minerals, Vit B_6, Vit B_5 Vit C and an n-6 or n-4 essential fatty acid, particularly GLA or DGLA, are administered in effective amounts to a person or other animal in need of such treatment.

3. As a composition, potassium and magnesium as minerals, Vit B_6 Vit B_5, Vit C and an n-6 or n-3 essential fatty acid (EFA), particularly GLA or DGLA, in unit dosage form effective in the treatment of stress and/or allergies, particularly seasonal and perennial respiratory allergies, optionally with an excipient or carrier.

4. A method, composition or use as above for treatment of hayfever or other seasonal and perennial respiratory allergies, allergic asthma, urticaria, hives, eczema, psoriases, or allergic conjunctivitis, or allergic equine conditions particularly obstructive pulmonary disease, laminitis or allergic eczema, or for treatment of toxic stress or specific stress related diseases including arthritis or essential hypertension.

5. A method, composition or use as above utilising an adult daily dose of potassium 10mg to 5000mg preferably 100mg to 1000mg and very prefarably 100mg to 400mg; magnesium 1.0mg to 1000mg preferably 10mg to 500mg and very preferably 50mg to 300mg; pyridoxine (Vit B_6) 0.1mg to 500mg preferably 5mg to 200mg and very preferably 10mg to 100mg; pantothenic acid (Vit B_5) 0.1mg to 1000mg preferably 10mg to 500mg and very preferably 50mg to 300mg; ascorbic acid (Vit C) 10mg to 5000mg preferably 100mg to 2000mg and very preferably 500mg to 1000mg; GLA or other n-6 or n-3 essential fatty acid 10mg to 5000mg preferably 100mg to 2000mg and very preferably 400mg to 1000mg.

Fig. 1

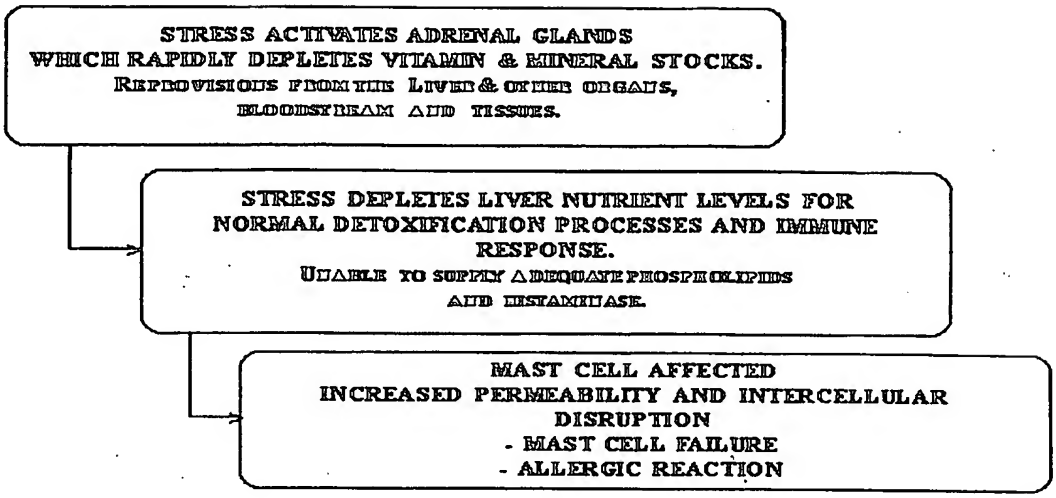


Fig. 2a

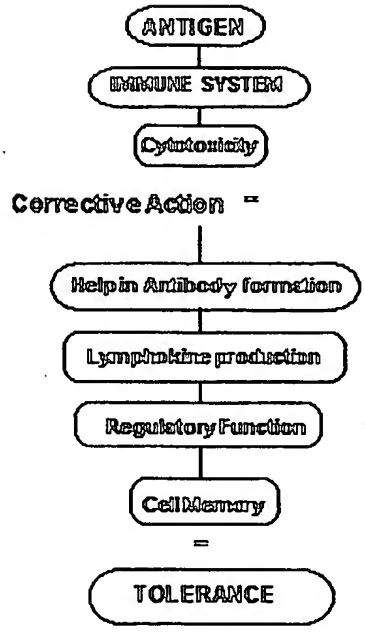
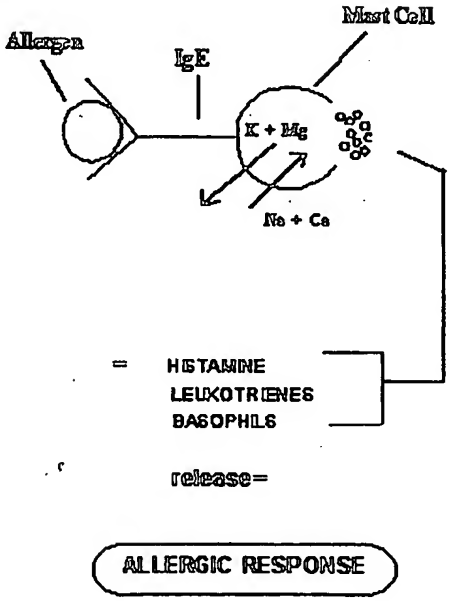


Fig. 2b



INTERNATIONAL SEARCH REPORT

Ir ational Application No
PCT/GB 98/02128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/06 //(A61K33/06,33:00,31:44,31:375,31:20,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 97 26897 A (PIPER EDWINA MARGARET) 31 July 1997 see page 9, paragraph 4 - page 11, paragraph 2	1-4
A	US 5 597 585 A (WILLIAMS ANDREW H ET AL) 28 January 1997 see claims	1-5
A	DATABASE WPI Section Ch, Week 9335 Derwent Publications Ltd., London, GB; Class B05, AN 93-273270 XP002082115 & CA 2 057 463 A (CREATIVE NUTRITION CANADA CORP), 12 June 1993 see abstract	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1998	05/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/02128

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 2, 4, 5
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/GB 98/02128

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9726897 A	31-07-1997	AU 1452597 A	20-08-1997
		CA 2218588 A	31-07-1997
		EP 0814816 A	07-01-1998
US 5597585 A	28-01-1997	NONE	

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(74) Agents: BANCHETTI, Marina et al.; Ing. Barzanò & Zanardo Roma S.p.A., Via Piemonte, 26, I-00187 Roma (IT).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/69426 A3

(54) Title: COMBINATION OF NICOTINIC ACID OR NICOTINAMIDE WITH RIBOFLAVIN FOR THE TREATMENT OF PRURITUS, ITCHING AND INFLAMMATION DISORDERS

(57) Abstract: Use of a combination of two vitamin compounds, i.e. riboflavin (also known as vitamin B_2) and nicotinic acid (also referred to as niacin) or, as an alternative thereto, the corresponding amide, i.e. nicotinamide or niacinamide (also known as vitamin PP) for the systemic treatment of various forms of itching, such as, e.g., pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections, as well as for the treatment of a number of non-infective internal affections of a substantially inflammatory nature, such as e.g., urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/455 A61K31/525 A61P17/00 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OTROKOV A N: "'New methods of vitamin B treatment of itching dermatoses in middle aged and aged patients!. Novye metody B-vitaminoterapii bol'nykh zudiashchimi dermatozami v pozhilom i starcheskom vozraste." VESTNIK DERMATOLOGII I VENEROLOGII, (1977 DEC) (12) 62-5. , XP000961650 abstract	1-21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	22/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 00/00196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

information on patent family members

Intr ional Application No
PCT/IT 00/00196

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(71)(72) Applicant and Inventor: VALLETTA, Giampiero [IT/IT]; Via Campidoglio, 188, I–03024 Ceprano (IT).

(74) Agents: BANCHETTI, Marina et al.; Ing. Barzanò & Zanardo Roma S.p.A., Via Piemonte, 26, I–00187 Roma (IT).

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Published

Without international search report and to be republished upon receipt of that report.

(54) Title: USE OF A VITAMIN COMBINATION FOR THE TREATMENT OF PRURITUS AND NON–INFECTIVE DISORDERS INVOLVING ITCHING AND/OR INFLAMMATION

(57) Abstract

Use of a combination of two vitamin compounds, i.e. riboflavin (also known as vitamin B_2) and nicotinic acid (also referred to as niacin) or, as an alternative thereto, the corresponding amide, i.e. nicotinamide or niacinamide (also known as vitamin PP) for the systemic treatment of various forms of itching, such as, e.g., pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections, as well as for the treatment of a number of non–infective internal affections of a substantially inflammatory nature, such as e.g., urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

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USE OF A VITAMIN COMBINATION FOR THE TREATMENT OF PRURITUS AND NON-INFECTIVE DISORDERS INVOLVING ITCHING AND/OR INFLAMMATION

SPECIFICATION

The present invention concerns the use of a vitamin combination for the treatment of pruritus and non-infective disorders involving itching and/or inflammation. More particularly, this invention relates to the use of a combination of two vitamin compounds, i.e. riboflavin (also known as vitamin B_2) and nicotinic acid (also referred to as niacin) or, as an alternative thereto, the corresponding amide, i.e. nicotinamide or niacinamide (also known as vitamin PP) for the systemic treatment of various forms of itching, such as, e.g., pruritus associated with renal insufficiency or failure or various forms of itching the etiology of which is not connected with organic lesions or with other primary pathologies, as well as for the treatment of a number of non-infective internal affections of a substantially inflammatory nature.

As it is known, the cutaneous sensation currently referred to as itching may be considered as a uniform response to a wide variety of physical and chemical stimuli, which may be of an endogenous or exogenous nature. Such stimuli act on the receptors of the free nerve endings located at the dermal-epidermal junction and around the hair follicles. It is currently believed that pain, temperature and touch are all sensations transmitted through the same pathways of non-myelinated free nerve fibers innervating human skin. A low-intensity stimulation of such fibers would cause pruritus while a more intense stimulation would turn into a real pain sensation. While being transmitted through the same sensory fibers, the neural impulses of itch have a frequency quite lower than the pain impulses; however, if scratching follows as a response to the itch stimulus, the frequency of the neural impulses increases with the intensity of scratching, and the corresponding sensation turns from itchy into painful.

As pointed out in the foregoing, itching may be induced by a great variety of circumstances, both physiologic and pathologic. Especially when it is generalized and associated with cutaneous lesions, such as vesicles and papules, itching is often the effect of a primary dermatological disease, and in many cases it represents the fundamental symptom for diagnosis. In the absence of cutaneous lesions, on the other hand, itching may originate in many cases from systemic disorders such as, e.g., neoplastic diseases, metabolic or endocrine disorders, renal, hematological or hepatic diseases, or also from allergic reactions, or from hypersensitivity to some medicaments. Lastly, in other cases itching appears to be the sole dominant chronic symptom, with no possibility of any clarification on the etiopathogenesis of this affection. In such cases, itching is normally referred to as "sine materia" pruritus, i.e. it represents a symptom of an unknown origin, which is not classifiable in the absence of identifiable cutaneous or extracutaneous alterations. The only objective, albeit secondary, signs of the concerned disorder are limited to traces of scratching such as linear excoriations and, if the situation lasts for a longer time, small secondary papules (i.e. papules due to scratching) and lichenification signs with hyperpigmentation in the most chronic cases.

The group of "sine materia" pruritus includes the itching manifestations occurring, without any connection with organic lesions or with systemic or skin diseases, in the external genital areas (such as vulvar and scrotal pruritus) and in the perianal area (scientifically referred to as pruritus ani), as well as pruritus of aged skin (i.e. senile pruritus). The latter is a generalized affection quite diffused among persons aged 65 or over. In this case, once the possible occurrence of skin diseases such as scabies, bullous pemphigoid, lichen planus and eczema, or the occurrence of systemic diseases characterized by pruritic symptomatology, such as those mentioned in the foregoing, have been excluded, the itching sensation has to be ascribed, actually, to the so-called pruritus of aged skin. Such condition is considered to be a consequence of desiccation of the skin. A dehydrated skin, generally combined with exposure to ambient conditions of low humidity and temperature, induces fine cracking and scaling in the skin of the elderly subject, with consequent dif-

fused and persistent itching.

The actual pathway through which the itching reaction is elicited has been investigated in several detailed studies, and several chemical mediators of itch, such as histamine, kallikrein, PAFs (platelet activating factors) and various endopeptidases (e.g., papain, trypsin, erythrocyte proteases, mast cell proteases, lysosomial enzymes) have been identified to date. In spite of that, the mechanism of itch induction has not been fully clarified at present. It is essentially for this reason that some agents successfully employed against some forms of itching, such as, e.g., antihistamines or steroidal drugs, are totally ineffective against other forms. The therapeutic approach adopted so far for the treatment of the "sine materia" pruritus forms, in particular for the treatment of senile pruritus and of itching of the anal and genital areas, consists of topically applying corticosteroidal drugs, antihistamines and skin moisturizers. However, none of these remedies turned out to be appreciably effective in the concerned cases.

Another type of pruritus against which, at present, no valid therapy has been found, in spite of the abundant information available about the supposed causes thereof, is the pruritus connected with renal insufficiency, usually referred to as uremic pruritus. The latter is one of the most distressing symptoms of renal insufficiency, affecting about 80% of the patients on renal dialysis, and is currently believed to be due to the building up of some pruritogenic substance in the body. Patients with chronic renal failure often exhibit cutaneous dryness, anemia, defects of homeostasis such as haematomas and ecchymoses, and secondary hyperparatyroidism (with itching and lesions due to scratching). The abundant use of emollients rarely results in significant relief. In some cases the symptoms are reduced when the patient undergoes dialysis, thereby suggesting that a pruritogenic substance has been removed. However, in many cases itching persists even after dialysis, and resists to all therapeutic attempts, both systemic and topical. Also against such types of pruritus the current therapeutic approaches consist of the administration of antihistamines or corticosteroids, mostly without any appreciable success.

It is therefore one object of the present invention to provide a thera-

peutic remedy effective for the treatment of the "sine materia" pruritus forms, as well as for the treatment of uremic pruritus, which allows to successfully resolve, by means of a pharmacological therapy consistently effective and free from adverse effects, such hitherto unresolved pathologic conditions. To achieve such purpose, in the frame of the research that lead to present invention, a particular combination of vitamins has been considered, i.e. the combination of nicotinic acid, i.e. 3-pyridinecarboxylic acid, also known as niacin (or, in the alternative thereto, the corresponding amide, i.e. nicotinamide, also known as vitamin PP) and riboflavin (also known as vitamin B_2).

The first ingredient of the above combination, i.e. nicotinic acid, is a well-known vitamin, naturally occurring in several animal and vegetal tissues, particularly in food sources such as meat, poultry, fish, liver, kidney, eggs, nuts, butter, milk and yeast. In human beings, nicotinic acid may also be synthesized from the amino acid tryptophan, but the latter source is normally insufficient to satisfy the dietary requirements for this vitamin. Actually, the alternative name vitamin PP (or P.P. factor, i.e. pellagra preventive factor) by which the said agent is known is due to its critical activity in the prevention of pellagra. The latter is a disease caused by vitamin deficiency, that occurs in dietary regimens poor in tryptophan (or, correspondingly, in niacin or in nicotinamide), such as a diet substantially based on maize and with a poor intake of animal proteins.

Nicotinic acid functions in the body only after conversion to either one of the physiologically active forms nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP). These serve as coenzymes for a wide variety of proteins that catalyze oxidation-reduction reactions essential for tissue respiration. Such biological process is actually the result of several oxidation-reduction reactions occurring within the cells, in particular in the mitochondria, aimed at oxidizing that part of material reaching the cells (through the blood circulation) in order to be employed for energy production. Among the various enzymes responsible for the oxidative processes (i.e. oxidoreductases), that perform their function by accepting a H_2 molecule from the substrate, the enzymes referred to as dehydrogenases cannot employ

molecular oxygen as an immediate acceptor of the hydrogen taken from the substrate, but have to use the pyridine coenzymes (i.e., NAD and NADP) as acceptors. Therefore, the presence of the said coenzymes is of a critical importance for the proper development of the biochemical cycles that produce energy from, e.g., sugars (i.e., glycolysis and Krebs cycle) or from fatty acids (i.e., beta-oxidation), and in the metabolic pathway leading to urea (ornithine cycle).

In view of the foregoing, the presence of suitable levels of nicotinic acid and/or niacinamide (or tryptophan) in the body is an essential requirement for a healthy skin, for the regular function of the gastrointestinal tract, for the maintenance of the nervous system as well as for the synthesis of the sex hormones. Symptoms of deficiency may be muscular weakness, generalized asthenia, loss of appetite, cutaneous eruptions, stomatites, insomnia, nausea and migraine. As pointed out in the foregoing, a severe deficiency leads to pellagra. The dosages of nicotinic acid, nicotinamide or suitable derivatives (such as methyl nicotinate) normally employed for the treatment of pellagra are of about 50 mg, by the oral route, up to ten times daily. In the event that the oral administration is impossible, intravenous injection of 25 mg of vitamin may be given two or more times daily.

It is also known that nicotinic acid and nicotinamide are effective in improving blood circulation and in lowering cholesterol levels. As far as the first mentioned effect is concerned, some products for topical administration containing nicotinic acid are available, having the function of topical rubefacient and analgesic, for the relief of muscular pain and rheumatism. In these products niacin assumedly performs the function of enhancing peripheral blood circulation, as it dilates the subcutaneous blood vessels after penetrating the skin.

As far as the second effect mentioned above is concerned, niacin is employed for systemic administration, i.e. by the oral or the parenteral route, at dosages quite above the dosage required for the prophylaxis and therapy of pellagra (namely, from 2 to 6 g per day) in preparations intended for the therapy of hyperlipidemia, for lowering cholesterol levels in the blood. At the large

doses required for this therapeutic indication, however, both nicotinic acid and nicotinamide have shown a number of adverse side effects, including gastro-intestinal disturbances (such as abdominal pain and nausea) hepatotoxicity, and, above all, flushing (cutaneous erythema) often accompanied by warmth, tingling and itching.

In order to reduce the said side effects while keeping the high dosages required for the antilipemic therapy, there have been proposed modifications of the nicotinic acid molecule, resulting in various derivatives thereof, as well as combinations of niacin or nicotinamide with other active ingredients or adjuvants, specific dosage forms and formulations. An example of such modifications is disclosed in EP-A-0349235 (and in the corresponding U.S. Patent No. 4,965,252), concerning an oral antihyperlipidemic composition of nicotinic acid wherein the active ingredient is mixed with guar gum and, optionally, with food-grade organic acids and/or pharmaceutically acceptable mineral salts, as well as other suitable adjuvants. The combination with guar gum reportedly affords a preparation for oral administration which eliminates the undesirable flushing and itching side effects of high dose niacin while effectively lowering cholesterol levels. In addition, the proposed combination is said to only require an effective dosage of niacin of 1.2-1.5 g per day, lower than the recommended daily dose of niacin when used alone as an antilipemic agent.

Another example of systemic preparation exploiting the activity of nicotinic acid for the treatment of hyperlipidemias while attempting, at the same time, to reduce the adverse side effects thereof, is disclosed in the international patent application WO-A-9632942. The latter discloses a combination of a hypolipemic amount of nicotinate with a non-steroidal anti-inflammatory drug (NSAID), preferably in a sustained release form. According to the disclosure, the NSAID is effective in reducing the flushing side effect associated with the use of niacin when administered as an antilipemic agent.

In spite of the fact that one of the most usual adverse effects of high dosage nicotinic acid and niacinamide is itching, the concerned agents have also been proposed, mostly in preparations for topical administration, for use in the therapy of cutaneous affections wherein itching is one of the typical

symptoms. For instance, the international patent application WO-A-9852297 discloses dermatological and cosmetic compositions based on nicotinamide, niacin, or ester derivatives thereof (methyl nicotinate being particularly preferred), which are applied topically on the skin to treat a number of skin conditions including acne, age spots, fungi, itching, pain and itching from insect bites, cellulite, varicose veins, stretch marks and burns. The list of affections that may be treated with the claimed composition, in addition to being extremely generic, is not supported by any experimental data, nor any chemical test is reported that may allow to evaluate the therapeutic effects obtained with the use of the topical preparation disclosed.

On the other hand, the use of nicotinamide or nicotinic acid for the treatment of acne vulgaris, both by topical and by systemic administration, has previously been disclosed in the U.S. Patent No. 4,505,896. As far as the oral therapy is concerned, said document proposes the oral administration of dosages comprised between 100 and 600 mg per day (in divided doses taken two to four times daily). Such doses of niacin/nicotinamide are, actually, of the same order of magnitude as the dose required for therapy or prophylaxis of vitamin PP deficiency, and the problem of the flushing side effect is apparently not relevant at such low doses.

In the frame of the studies that lead to the instant invention, it has been ascertained, as a first step, that the systemic administration of niacin or niacinamide at dosages quite lower than for the therapy of hypercholesterolemia - namely at the dosage typically employed in the use of the same agents for the prevention and therapy of pellagra - on one hand does not lead to the undesired side effects of flushing and itching reported for the high dosages but, on the other hand, is not appreciably effective in combating the pruritus forms referred to in the foregoing. As a matter of fact, according to the clinical experimentation carried out and partially reported further on, uremic pruritus and itch affecting patients on renal dialysis, as well the "sine materia" pruritus forms (such as pruritus ani, pruritus vulvae, and pruritus senilis) did not show to be sufficiently responsive to the administration of preparations based on nicotinamide or niacin alone.

It has been found, however, that the desired effect is obtained when niacin or nicotinamide are administered systematically in combination with another known vitamin compound, i.e. riboflavin or vitamin B_2.

In this connection, the U.S. Patent No. 5,496,827 teaches compositions for topical application on the skin, wherein the main active ingredient, i.e. methyl nicotinate, may be combined with various vitamins, minerals and other nutrients, including, inter alia, riboflavin. The resulting topical compositions are proposed for use in the treatment of various conditions that may be treated by means of topical applications to the affected areas, such as muscular pain, acne, eczema, or for stimulating the hair growth, removing senile lentigines (brown spots) and enhancing fingernail growth. Also in this case, the prior art points out that an excessive increase of the methyl nicotinate level "tends to produce a rather pronounced pruritus (itching of the skin)". The concerned document, however, mentions riboflavin as one of the many vitamins and trace elements that may be added to methyl nicotinate in order to be carried through the skin by transdermal delivery, as the alleged function of methyl nicotinate is to promote transdermal delivery.

With reference to the second active ingredient of the present invention, i.e. riboflavin (7,8-dimethyl-10-(D-ribo-2,3,4,5-tetrahydroxypenthyl)isoalloxazine, also such compound is a nutritional factor of a primary importance, that is found mainly in milk, eggs, cheese, liver, heart, kidney and leafy vegetables. Riboflavin carries out its biological function in the body in the form of one or the other of two coenzymes, i.e. riboflavin phosphate, commonly called flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD). Similarly to the two pyridine coenzymes referred to in the foregoing (i.e., NAD and NADP), FMN and FAD co-operate with the respiratory flavoproteins in oxidizing the substrate by accepting a hydrogen molecule from the substrate. Contrary to NAD and NADP, however, FMN and FAD may yield said hydrogen directly to molecular oxygen. In addition, the oxidoreductive potential of FMN and FAD is such that these two compounds can oxidize the reduced pyridine coenzymes: actually, the function of flavoproteins (having, as pointed out before, FAD and FMN as coenzymes) is on one hand to directly oxidize the

substrates and, on the other hand, to assist in the function of the pyridine enzymes, by reoxidizing them once they have become reduced by reaction with a substrate.

In view of the foregoing, considering that, in practice, the pyridine coenzymes (NAD and NADP) can perform their function only in the presence of flavoproteins, and thus in the presence of riboflavin, it will be apparent that the presence of both niacin and riboflavin is necessary for an efficient working of the biochemical mechanisms governing the cellular metabolism. Without wishing to be bound by any particular theory concerning the mechanism of action of the proposed combination of active agents, it is postulated that both niacin and riboflavin play a critical role in the metabolism of the mast cells. A deficiency of any one of the said agents would negatively affect the energy-production step of the metabolic chain leading to activation of these cells, that is mostly responsible for the release of biochemical mediators of the itching and inflammatory responses. As known, mast cells are found in organs rich in connective tissue, such as the skin and the respiratory and gastrointestinal tracts, and are characterized by the presence of granules that may be secreted by the mast cell upon activation of the latter, thus releasing a number of the above mentioned mediators, including histamine.

According to the present invention, it has been considered that once the mast cells are activated - by a variety of mechanisms, including binding of their membranes with immunoglobulins E (IgEs) and exposure of the mast cell to an antigen - there occurs within the mast cell a series of enzymatic reactions comprising an energy-requiring step and ending with the degranulation of the mast cells and the release of preformed or newly-generated mediators. The preformed mediators, that are stored in the above-mentioned granules, include histamine (which, inter alia, causes smooth muscle contraction and itching, enhances the venular permeability and increases the airway resistance), while other unstored mediators, that are generated upon activation of the mast cells and have the capacity to alter the venular permeability and to contract smooth muscles in a variety of organs, include SRS-A (slow-reacting substance of anaphylaxis) and PAFs (platelet activating factor(s)).

In view of the foregoing, in the light of the clinical tests results presented further on, it may reasonably be postulated that both the "sine materia" pruritus forms, which are not due to any primary dermatological or internal affection, and uremic pruritus, which is a manifestation of unknown etiology connected with renal insufficiency, are caused by some energy-controlled alterations in the metabolic pathway leading to the secretion of biochemical mediators from mast cells, and that a the systemic administration of a suitable dosage of niacin or nicotinamide and riboflavin would provide the body with the necessary amounts of NAD/NADP and FAD/FMN to properly modulate the mast cells activity.

As a further object of the instant invention, other affections of a non-infective etiology characterized by itching and/or inflammation (phlogosis) such as, e.g., urticaria and angioedema, bronchial asthma, allergic rhinitis and oculorhinitis, have been considered, in the light of the above etiopathogenetic theory, in order to provide a systemic therapy exploiting the same combination of active ingredients.

As it is known, urticaria is a pruritic dermatosis characterized by the formation of circumscribed, raised, erythematous and usually pruritic areas of edema. Such lesions have a rosy-red appearance with a white central area, and are surrounded by an erythematous halo. The single wheals may have a round, elliptic or variously contoured shape, and may evolve in a few days or weeks (acute urticaria) or in several weeks or months (chronic urticaria). When the edematous process extends into the dermis and/or subcutaneous or submucosal layers, the relevant affection is known as angioedema. Urticaria and angioedema may occur in any position together or individually. Both affections may be due to several etiologic factors of an immunologic nature (such as, e.g., hypersensitivity to pollens, foods, drugs, etc.), or of a non-immunologic nature (e.g. non-IgE-dependant intolerance to various therapeutic and diagnostic agents, such as the well-known reactions to aspirin and related non-steroidal anti-inflammatory agents). However, in the great majority of cases, urticaria/angioedema is of unknown cause, and is currently referred to as idiopathic urticaria.

Asthma is a respiratory disorder characterized by recurring episodes of dyspnea, wheezing, coughing and viscous mucoid bronchial secretions, caused by obstruction of the airways by excessive mucous production and edema of the respiratory mucosa. These reactions are believed to result from an increased sensitivity of the bronchial tree to stimuli of various origin, such as physical or emotional stress, inhalation of powders or pollutants or contact with allergens or with some drugs. Also in this case, the pathogenesis of the disease is unclear, and the actual mechanism by which asthma develops is unknown. However, according to the most diffused position, bronchial asthma is to be considered an inflammatory disease. In particular, allergic asthma is caused by the exposure of the bronchial mucosa to an inhaled airborne antigen. The latter causes the production of antibodies (IgEs) that bind to mast cells thereby activating such cells as explained in the foregoing. The release of histamine by the activated mast cells stimulates contraction of the bronchial smooth muscle and causes mucosal edema. The current therapy for asthma may include elimination of the causative agent, aerosol or oral bronchodilators, beta-adrenergic drugs, methylxanthines, sodium cromoglycate and short term use of corticosteroids.

Allergic rhinitis is an inflammation of the nasal passages, usually associated with nasal obstruction and discharge, as well as itching of the nose, caused by a localized sensitivity reaction to an allergen like dust, animal dander, or an antigen such as pollen. When the itching symptom extends to the eyes, accompanied by lachrymation, the disease is more properly referred to as oculorhinitis. The conventional treatments include the topical or systemic administration of antihistamines, avoidance of the antigen and hyposensitization by injection of diluted antigen in gradually increasing amounts.

In accordance with the invention it has been found that the above affections, as well as other affections characterized by a substantially inflammatory nature and often accompanied by the itching symptom, may be successfully treated by means of the systemic administration of the proposed vitamin combination.

Accordingly, the present invention specifically provides the use of a

combination of nicotinic acid or nicotinamide with riboflavin for the manufacture of a medicament for systemic administration for the treatment and/or the prophylaxis of pruritus and non-infective disorders involving itching and/or inflammation. Specifically, the forms of pruritus against which the proposed combination is particularly effective include itch associated with renal insufficiency or failure (i.e. uremic pruritus) and pruritus forms that are not connected with primary organic affections, such as itching of aged skin (i.e., senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus. As to the non-infective disorders involving itching and/or inflammation, the proposed combination is particularly useful for combating urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

For the therapeutic indications according to the present invention, the two active ingredients are to be systemically administered at a dosage comprised between 0.5 and 750 mg/day of niacin or of nicotinamide and between 0.1 and 250 mg/day of riboflavin. Preferably, the said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin), optionally in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration. The preferred ratio is 20:1 (niacinamide : riboflavin). According to a particularly effective therapeutic protocol, 50 mg of nicotinamide + 2.5. mg of riboflavin are orally administered twice daily, and the treatment is continued until the itching or the inflammatory affection has totally disappeared. Thereafter, in some particular instances, the treatment is continued with half the dosage of the vitamin combination, for about 15 more days.

The compounds according to the invention may be administered through different systemic routes, e.g. orally or parenterally. For such types of administration the active ingredients may be incorporated in conventional pharmaceutical preparations, in solid or liquid dosage forms. The latter may contain the adjuvants usual in the pharmaceutical art such as, for instance, sweeteners, flavors, colors, coatings and preservatives, inert diluents such as calcium carbonate, sodium carbonate, lactose and talc, binders such as starch, gelatin and polyvinylpyrrolidone, suspending agents such as methyl

cellulose or hydroxyethyl cellulose and wetting agents such as lecithin, polyoxyethylene stearate and polyoxyethylene sorbitan monooleate, reducing agents such as ascorbic acid and salts thereof. The preparations for parenteral administration (in particular, to be injected through the intravenous or the intramuscular route) may also contain the active ingredients dissolved or suspended in distilled water, together with the common pharmaceutically acceptable excipients.

A particularly effective therapeutic protocol according to the invention, for the treatment of all of the itching and inflammatory forms specified above but uremic pruritus is as follows: 1st phase: 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily by oral administration, up to the total disappearance of the symptom; then continue with 50 mg of nicotinamide + 2.5 mg of riboflavin once daily for 15 days; 2nd phase (optional): 50 mg of nicotinamide + 2.5 mg of riboflavin once daily for 15 days a month, for prophylactic purposes. It is advisable to take the medicament by the oral route, after the main meals, with abundant water (at least half a glass). In the event that the treatment is discontinued and the symptoms revert, it is necessary to start again from the 1st phase.

A therapeutic protocol suited to the treatment of uremic pruritus (without dialysis) is as follows: 1st phase: 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily by oral administration, up to the total disappearance of pruritus; then continue with 50 mg of nicotinamide + 2.5 mg of riboflavin three times a week; 2nd phase (optional): 50 mg of nicotinamide + 2.5 mg of riboflavin three times a week for 15 days a month. Also in this case, the preferred form of administration is the oral form, and also in this case if the therapy is discontinued and itching appears again, the protocol will have to be restarted from the beginning. In the treatment of uremic subjects who currently undergo dialysis the protocol is the same as for the 1st phase above, but the continuation of the treatment with half the dose will take place starting after each dialysis treatment (also in this case, after the meal and with abundant water).

As pointed out before, as an alternative to oral administration the parenteral route may be exploited, with a preferred dosage of 20 mg of nicoti-

namide and 1 mg of riboflavin once or twice daily.

According to another specific aspect thereof, the present invention provides a composition for systemic administration for the treatment and/or the prophylaxis of pruritus and non-infective disorders involving itching and/or inflammation, containing, as the active ingredients, a combination of nicotinic acid or nicotinamide with riboflavin. Particularly preferred features of the said compositions are recited in the dependent claims. It is evident, however, that the two active ingredients of the invention do not necessarily have to be contained in a single preparation, as they can be administered separately, provided that the dosage and therapeutic protocol are as prescribed in the foregoing.

Some experimental results obtained according to the present invention, including clinical data concerning the performance of the proposed combination in comparison with the use of nicotinic acid or nicotinamide alone, are reported below for merely illustrative purposes.

1st series of tests - Treatment with the nicotinamide-riboflavin combination

1st case - 67-year-old male subject in renal dialysis three times weekly - At the start of the test, the patient had been on dialysis three times a week for about two years, each treatment lasting 4 hours. For about 4 years, the patient had been complaining of a diffused itching. The latter was quite moderate at the beginning, but had been gradually increasing in intensity, and had become quite unbearable. Upon interviewing the specialists responsible for the renal treatment, he was given antihistamines for about six months with no appreciable result. As a consequence, the patient had discontinued the antihistamine treatment.

Thereafter, the patient was treated with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, by oral administration. After 5 days from the start of this therapy, itching had disappeared. The patient continued the same therapy for about 15 days, and thereafter the dosage was reduced to one-half, the administration occurring after the dialysis treatment. The subsequent checks, performed every month, showed that itching had totally disappeared.

2nd case - 65-year-old male subject with chronic renal failure - The patient had been suffering from chronic renal failure for about 4 years. The nitrogen level of his blood was 105 mg/dl, while the level of his serum creatinine was 3 mg/dl. The patient was being treated by a nephrologist. About 15 months before, he started to report a diffused increasing pruritus, that had become unbearable about 9 months before. Every therapeutic approach proposed and carried out by the kidney specialist resulted in no appreciable relief.

The patient was then treated orally with a combination of 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily. After 6 days itching had totally disappeared, and the treatment was continued for 10 days more. Thereafter, the dosage was reduced to one half, still administered by the oral route, for 15 days a month. At the subsequent checks, carried out every month, the patient reported a total absence of itching.

3rd case - 67-years-old female subject with senile pruritus - The patient had been complaining for about 3 years of a diffused itching, which had become increasingly intense. At first, she consulted her physician, who addressed her to a dermatologist. As no cutaneous pathologies had been evidenced, the patient was visited by a specialist in internal medicine, who diagnosed a senile pruritus and prescribed some hygienic measures and antihistamines, from which the patient had drawn no benefits.

The patient was then treated by oral administration of 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily. After 5 days the itching had totally disappeared, and the treatment was continued for 10 days more. Thereafter, the therapy was reduced to half the dosage, for 15 days a month. At each subsequent check-up, the patient did not report any itching.

4th case - 46-years-old female subject with anal and vulvar pruritus - The localized symptomatology was quite severe since about two years before. As a first attempt, a gastroenterologist had been consulted for the anal itching, and thereafter a gynaecologist had been consulted for the vulvar itching. Neither specialist could detect any objective disorder falling within his competence. In order to mitigate the disturbance, various topical treatments with non-steroidal anti-inflammatory drugs, corticosteroids and antimycotic agents

had been prescribed, as well as a systemic treatment with antihistamines. No treatment brought about any improvement in the patient's condition.

The patient was then treated with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, by oral administration, and after 7 days itching had disappeared. The treatment was continued for 12 more days, and then it was reduced to half the dosage, for 15 days a month. At each subsequent monthly check-up the patient always reported a total absence of itching.

5th case - 50-years-old male subject with acute urticaria.- After collecting mushrooms in a wood, the patient had been complaining for eight days of a serious itching at his forearms and torso. At the clinical examination, the patient showed, both on his forearms and on the front and back of his chest, erythematous circumscribed lesions having wavy margins, remarkably raised with respect to the rest of the surrounding skin. Traces of superficial lesions were present, apparently due to scratching. Upon being diagnosed an acute urticaria, the patient was treated with systemic antihistamines and corticosteroids, from which he could not draw any benefit.

The patient was then treated orally with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily. After 2 days the patient's condition had already remarkably improved, and after 3 more days itching had entirely disappeared, although some moderate erythematous lesions were still visible. In this case the therapy was continued for 10 more days and then it was finally discontinued.

6th case - 46-years-old female subject with recurrent urticaria - The patient, who lives in the countryside, had been complaining for 15 years of a phytodermatitis that manifested itself with episodes of urticaria. The latter appeared with itching and reddish wheals of 3-4 cm diameter, diffused, initially, only on the parts of the body that came in contact with an unidentified grass, and progressively extending to the rest of the body. When such episodes, usually lasting for 12 days, occurred, the patient used to take antihistamines and corticosteroids, however with no appreciable relief.

Then, at the beginning of one of such episodes of urticaria the patient was administered, by oral route, 50 mg of nicotinamide + 2.5 mg of riboflavin

twice daily. As a result, itching decreased and disappeared in the following 4-5 days. Thereafter, the patient continued to take half a dose of the above agents for 15 days a month, and the subsequent contacts with the grass of her garden did not result in any skin discomfort.

7th case - 28-years-old female subject with bronchial asthma - The patient had been suffering for about 10 years from recurrent episodes of bronchial asthma, in the spring period (i.e., from April to June). During each of said episodes, the patient experienced coughing, expiratory dyspnea, suffocation feeling. At the end of said episodes, that usually lasted about one hour, the patient excreted a dense and viscous material. She used to take antihistamines regularly in spring, sometimes in combination with theophyllins, with a quite poor relief.

Starting from mid-March, the patient was then treated with 50 mg of nicotinamide + 2.5 mg of riboflavin, twice daily, by oral administration. The treatment was continued as such for 4 months on end and then discontinued. No episodes of bronchial asthma occurred during the whole spring period.

8th case - 32-years-old male subject with bronchial asthma - The patient had started to suffer from respiratory disturbances (i.e. coughing, dyspnea) since he was 15. Such disturbances entailed a diagnosis of bronchial asthma. They appeared in the late spring (i.e. mid-April) and lasted until the end of June. Since the said diagnosis was made, the patient was treated with antihistamines. Corticosteroids and theophyllins were administered during the acute episodes. Such therapy had constantly resulted in a partial result.

The patient was then orally treated, starting from mid-April, with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, for 3 months on end. During the said spring period, no episodes of asthma were ascertained. Thereafter, the therapy was discontinued until the following spring.

9th case - 40-years-old male subject with allergic oculorhinitis - The patient suffered from allergic oculorhinitis, which manifested itself with sneezing, lachrymation, pharyngeal pain. He was also allergic to gramineae. The symptoms started in April and lasted until June. He had been treated with antihistamines during the critical period, but the symptoms, in spite of the

treatment, were only attenuated.

The patient was then treated, starting from the beginning of April, with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, by oral administration. The treatment was continued for 15 days, and then the dosage was reduced to one half up to the end of June. During this period no symptoms of allergy were detected.

10th case - 12-years-old male subject with allergic rhinitis - The patient had been suffering for 6 years from allergic rhinitis, the symptoms of which were nasal discharge, sneezing and nasal obstruction. Such symptoms occurred in spring and during this period the patient was treated, with unsatisfactory results, by antihistamine therapy.

Starting from mid-March, the patient was then treated with oral administration of 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily. The same dosage was administered for 10 days, and then it was reduced to one half, and continued up to the end of June. During the whole period, the patient reported no symptoms that could be ascribed to allergic rhinitis.

2nd series of tests - Treatment in two phases: first with nicotinamide only and with the nicotinamide-riboflavin combination

1st case - 78-years-old male subject on renal dialysis three times weekly - The patient had been on dialysis three times a week for about 3 years, each treatment lasting 4 hours. For about two years and a half the patient had been complaining of a diffused itching, at the torso and on the upper and lower limbs. In order to try to overcome this problem he was prescribed a hyposodic diet that, in addition to causing arterial hypotension with syncopae episodes, did not afford any beneficial results as far as itch was concerned. Then, the patient was given antihistamines of various types, again with no appreciable results. Lastly, he underwent an additional 3 hours dialysis treatment each week, with carbon filter, for four weeks on end. Also this attempt was unsuccessful.

When starting the treatment with nicotinamide, itching persisted night and day, preventing the patient from sleeping. When clinically examined, the

patient did not show any cutaneous alterations that could explain such itching, but several lesions due to scratching were present, diffused on the whole body, consisting in linear excoriations. Some of such lesions appeared to be older, with scabs due to previous bleeding. The treatment was started with 50 mg of nicotinamide twice daily, to be taken orally after the main meals. After one month and a half, pruritus had sensibly decreased. The patient continued to take 50 mg of nicotinamide after dinner for 15 more days, and then he took 50 mg of the same agent only on the day of the dialytic treatment. At the subsequent check-up, after one month, the patient still complained of some moderate itching.

Thereafter the patient was treated with the combination of 50 mg of nicotinamide + 2.5 mg of riboflavin, twice daily. Itching disappeared in 5 days, and did not revert any more.

2nd case - 70-years-old male subject on renal dialysis for renal failure - The patient had been on renal dialysis for about 18 months, to treat a terminal chronic renal failure. He had been complaining of a diffused pruritus extending on the whole body, which he felt during the day, but even more intensely during the night. Upon consulting the specialists of the hospital where he was undergoing dialysis, the patient did not receive any treatment that could alleviate his pruritus.

Upon undergoing an oral treatment with 50 mg of nicotinamide twice daily for 45 days on end, the patient achieved an appreciable reduction of the symptom. Thereafter, he was treated with half dose of the same agent for 15 more days, and then the treatment was finally discontinued. After 15 days, itching had started again to gradually increase.

Then the patient underwent the therapy according to the invention, with an oral administration of 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily. After 6 days, itching had totally disappeared. The treatment was continued for 15 more days with half the dose, and then it was discontinued. At the subsequent check, after 2 months, the patient did not report any itching.

3rd case - 45-years-old female subject with persistent anal vulvar pruritus - The concerned symptoms had persisted for about 2 years. Having con-

sulted first a gastroenterologist, the patient underwent a rectoscopy with biopsies, which did not show the presence of any pathology that could explain the itching. A rectal cortisone foam, prescribed as a possible remedy, did not result in any relief. As to the vulvar pruritus, the patient had consulted a gynaecologist who did not detect any particular pathology. She was then prescribed a therapy with vaginal douches with mild disinfectants and cortisone creams, which did not reduce itching at all. The patient was then treated with antihistamines, with no appreciable benefit. As she suffered from an allergy to antibiotics, she had also undergone all of the necessary allergy tests, but no particular allergies were evidenced. Later, a persistent itching had also appeared on the patient's face, albeit with no cutaneous lesions.

Then, the patient was given a therapy with 50 mg of nicotinamide twice daily, by oral administration, after the main meals. After 60 days itching was moderate. The patient continued to take 50 mg of nicotinamide daily, after dinner, for 15 days, and then she discontinued the treatment. After 15 days itching started to increase again, quite slightly at first, and then more remarkably.

The patient then started the oral therapy with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, and itching totally disappeared after 15 days. The treatment was then continued for 15 more days, with half the dosage, and then finally discontinued. At the subsequent check-up, after 2 months, the patient did not complain of any itching.

4th case - 65-years-old female subject with senile pruritus - The patient had been suffering for about 2 years and a half from a diffused continuous itching at the torso and on the upper and lower limbs. Such itching became sometimes milder for one week without disappearing completely. Clinical analysis and X-ray examinations did not show the presence of any particular disease. Upon consulting some physicians, the patient underwent treatments with antimycotic, antihistamines and corticosteroids, albeit with no appreciable improvement. When the clinical test was started, the examination revealed the absence of any cutaneous alterations that could explain the itching, and the diagnosis of senile pruritus was made. Diffused lesions due to scratching were

present.

The patient was then orally treated with 50 mg of nicotinamide twice daily, after the main meals, and after 40 days pruritus was quite mild. The treatment was continued with half the dose for further 15 days and then it was finally discontinued. After about 10 days, itching had started again to increase.

Then, the patient was treated with 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, by oral administration, and after 4 days itching had disappeared. The treatment with half the dose was continued for 15 days, and then it was discontinued. At the check-up, after 2 months, the patient reported to suffer no more from hitching.

5th case - 63-years-old male subject with chronic renal insufficiency - The patient had been suffering for about 5 years from chronic renal insufficiency, his serum creatinine level having been 3 mg/dl for about one year and a half. Thus, the patient was on a hypoproteic diet. Since about 2 years before, the patient had been affected with diffused itching of medium seriousness. He was prescribed antihistamines by the nephrologists who were treating him, and he continued such therapy for some time with no relief at all.

The patient was then treated with 50 mg of nicotinamide twice daily, orally administered after the main meals, and after 35 days he complained of some moderate itching. He had then discontinued the treatment. After about 10 days, itching had started to increase again.

Then, the treatment was changed to 50 mg of nicotinamide + 2.5 mg of riboflavin twice daily, by oral administration, and after 5 days itching had totally disappeared. At the subsequent check-up, after 2 months, the patient did not complain of any itching.

3rd series of tests - Treatment with nicotinamide alone

1st case - 68-years-old male subject on renal dialysis three times weekly - The patient had been on dialysis three times a week for about 15 months, each treatment lasting 4 hours. He had been diagnosed chronic terminal renal insufficiency. He had been suffering from itching for about 3 years, at first at his upper limbs and then, gradually, on the whole body. The intensity

of itching was steeply increasing, and no exterior signs could explain such affection. The nephrologists who were treating him had prescribed, at first, warm baths in order to moisten the skin, and then, as the symptoms were increasing, antihistamines. However, the patient could draw no benefit from such therapy.

Thereafter the patient was treated with 50 mg of nicotinamide twice daily, by the oral route, and after 65 days itching had only become milder without disappearing. The patient continued to take 50 mg of nicotinamide after each dialysis treatment. At each subsequent check-up, every 2 months, the patient complained of a persistent pruritus of a reduced intensity.

2nd case - 61-years-old male subject with renal insufficiency - The patient had been suffering for about 3 years of renal insufficiency that was becoming increasingly serious, and was being treated by a nephrologist. The nitrogen level of his blood was 100 mg/dl, while the level of his serum creatinine was 2.8 mg/dl. About 10 months before he started to complain of a diffuse pruritus of serious intensity, which did not regress with the conventional therapies adopted by the specialists.

Then, the patient was orally treated with 50 mg of nicotinamide twice daily. After 50 days, itching had become milder, without totally disappearing. In spite of the fact that the therapy with 50 mg/day of nicotinamide was continued, at the subsequent periodical checks the patient reported a moderate itching diffused on the whole body.

3rd case - 65-years-old female subject with senile pruritus - The patient had been suffering for about one year from a diffused itching. At first she had consulted a dermatologist, who excluded the presence of any cutaneous pathology. Then, the patient was examined by a specialist in internal medicine, who, after careful examination, could not evidence any kind of illness. As itching had increased in intensity, the patient had reverted to the dermatologist, who prescribed at first antihistamines, and then a thermal therapy. Thereafter, the diagnosis of senile itching was made.

The patient was then treated with 50 mg of nicotinamide twice daily by oral administration, and after 45 days itching had only slightly decreased. The

patient continued with the prescribed therapy, and, at the subsequent monthly checks, reported about the presence of a diffused moderate itching.

4th case - 48-years-old female subject with anal and vulvar pruritus - The patient had been complaining of the concerned symptoms for about of 18 months, the intensity of the symptoms being gradually increasing. Upon consulting a gynaecologist, no vaginal pathology was detected. However, she had been prescribed a topical therapy with cortisone and antimycotics, albeit with no benefit. A gastroenterologist, consulted for the anal pruritus, after performing a rectoscopy, did not find any pathology that could explain the itching symptoms. She was given a topical therapy based on a cortisone foam, from which she could not draw any relief.

Then the oral treatment with 50 mg of nicotinamide twice daily was carried out, and after 2 months a decrease of the symptoms was detected. At the subsequent monthly checks, the patient still complained of a moderate itching, in spite of the fact that she was still taking 50 mg/day of nicotinamide.

The foregoing experimental report clearly shows the superior effectiveness of the vitamin combination according to the invention in the therapy of several forms of pruritus and non-infective inflammatory diseases, in comparison with similar treatments suggested by the prior art, based on nicotinamide or niacin only.

The present invention has been disclosed with particular reference to some specific embodiments thereof, but it should be understood that modifications and changes may be made by the persons skilled in the art without departing from the scope of the invention as defined in the appended claims.

CLAIMS

1. Use of a combination of nicotinic acid or nicotinamide with riboflavin for the manufacture of a medicament for systemic administration for the treatment and/or the prophylaxis of pruritus and non-infective disorders involving itching and/or inflammation.

2. Use according to claim 1, wherein said medicament is for the treatment and/or the prophylaxis of pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections.

3. Use according to claim 2, wherein said pruritus forms that are not connected with primary organic affections are chosen from the group consisting of itching of aged skin (i.e. senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus.

4. Use according to claim 1, wherein said medicament is for the treatment and/or the prophylaxis of a disorder chosen from the group consisting of urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

5. Use according to any one of claims 1-4, wherein said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin), optionally in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration.

6. Use according to claim 5, wherein said combination consists of nicotinamide and riboflavin in a ratio by weight of 20:1.

7. Use according to any one of claims 1-6 for the manufacture of a medicament for oral or parenteral administration.

8. A method for the treatment and/or the prophylaxis of pruritus and non-infective disorders involving itching and/or inflammation in a subject in need of the same, said method comprising systemically administering to the said subject an effective amount of nicotinic acid or nicotinamide and an effective amount of riboflavin.

9. The method according to claim 8, wherein said medicament is for the treatment and/or the prophylaxis of pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections.

10. The method according to claim 9, wherein said pruritus forms that are not connected with primary organic affections are chosen from the group consisting of itching of aged skin (i.e. senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus.

11. The method according to claim 8, wherein said medicament is for the treatment and/or the prophylaxis of a disorder chosen from the group consisting of urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

12. The method according to any one of claims 8-11, comprising systemically administering to the said subject an effective amount of a combination of nicotinic acid or nicotinamide and riboflavin, optionally in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration.

13. The method according to claim 12 wherein said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin).

14. The method according to claim 13, wherein said combination consists of nicotinamide and riboflavin in a ratio by weight of 20:1.

15. The method according to any one of claims 8-14, wherein said systemic administration is by the oral route or by the parenteral route.

16. A composition for systemic administration for the treatment and/or the prophylaxis of pruritus and non-infective disorders involving itching and/or inflammation, containing, as the active ingredients, a combination of nicotinic acid or nicotinamide with riboflavin.

17. The composition according to claim 16, for the treatment and/or the prophylaxis of pruritus associated with renal insufficiency or failure (i.e. uremic pruritus), and of pruritus forms that are not connected with primary organic affections.

18. The composition according to claim 17, wherein said pruritus

forms that are not connected with primary organic affections are chosen from the group consisting of itching of aged skin (i.e. senile pruritus), vulvar pruritus, scrotal pruritus and anal pruritus.

19. The composition according to claim 16, for the treatment and/or the prophylaxis of a disorder chosen from the group consisting of urticaria and/or angioedema, asthma, allergic rhinitis and allergic oculorhinitis.

20. The composition according to any one of claims 16-19, wherein said combination consists of nicotinic acid or nicotinamide and riboflavin in a ratio by weight of from 40:1 to 10:1 (nicotinic acid or niacinamide : riboflavin), in a pharmaceutically acceptable vehicle or carrier suitable for systemic administration.

21. The composition according to claim 20, for oral administration or for parenteral administration.